IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

LIFE TECHNOLOGIES CORPORATION, and APPLIED BIOSYSTEMS, LLC,	§	
Plaintiffs	§	
vs.	§	**CIVIL ACTION NO. 2:09-cv-00283**
BIOSEARCH TECHNOLOGIES, INC., BIO-SYNTHESIS, INC., and EUROFINS MWG OPERON INC.,	§	
Defendants.	§	

DEFENDANTS BIOSEARCH TECHNOLOGIES, INC. AND EUROFINS MWG OPERON INC.'S CLAIM CONSTRUCTION BRIEF RESPONDING TO PLAINTIFFS' OPENING CLAIM CONSTRUCTION BRIEF

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I. INTRODUCTION

Defendants Biosearch Technologies, Inc. ("Biosearch") and Eurofins MWG Operon, Inc. ("Eurofins") (collectively, "Defendants") submit this brief in support of their proposed constructions of certain claim terms in the patents-in-suit: U.S. Patent Nos. 5,538,848 ("the '848 patent"), 5,723,591 ("the '591 patent"), 5,876,930 ("the '930 patent"), 6,030,787 ("the '787 patent"), and 6,258,569 ("the '569 patent") (collectively, the "Patents-in-Suit") and in response to Life Technologies Corporation ("Life Tech") and Applied Biosystems, LLC's ("ABI") (collectively, "Plaintiffs") Claim Construction Brief ("Pls.' Brief"). The Patents-in-Suit are continuations or continuations-in part of the '848 patent.

Defendants propose their constructions based upon an examination of the entire intrinsic evidence and, when particularly relevant, extrinsic evidence. While Plaintiffs often focus on one particular piece of evidence, *e.g.*, a quote from the specification, to support their proposed constructions, Defendants properly consider all of the evidence to determine the claim term meanings. Defendants have followed the Federal Circuit's guidelines by beginning with the claim language, then considering the specification, the prosecution history, and, when particularly appropriate, extrinsic evidence to determine the accurate meaning of each claim term at issue.

II. BACKGROUND

The technology at issue relates to dual-labeled probes. Dual-labeled probes are single-stranded oligonucleotides with a reporter bound to one nucleotide and a quencher bound to another nucleotide. Biosearch is one of the leading producers of dual-labeled probes for polymerase chain reactions ("PCR"). Biosearch has been innovating oligonucleotide technology since the 1980's and invented Black Hole Quencher® probes, a standard product in the industry,

used and licensed by numerous biotechnology companies. Eurofins is an international provider of DNA sequencing services, DNA synthesis products and bioinformatic services for academic and industrial research.

Defendants agree with Plaintiffs' description of the general science of DNA. However, Defendants do not agree with any of Plaintiffs' statements regarding their purported invention of "real time" detection of dual-labeled probe nucleic acid detection reactions, such as PCR. For background, PCR amplification reactions utilize a number of thermal cycles (for example, 30 cycles) to generate multiple copies of a nucleic acid product, *e.g.*, DNA. In 1994, dual-labeled probe PCR reactions were monitored only at the completion of the reaction, measuring the cumulative amount of the replicated DNA at the end of the 30 cycles. In 1996, Plaintiff ABI introduced the ABI Prism 7700 machine, which allowed monitoring during the reaction, *i.e.*, during each cycle, as well as at the end of the full reaction. Plaintiff ABI's own marketing materials and a publication by the first named inventor of the Patents-in-Suit affirmatively state that the ability to monitor PCR reactions of dual-labeled probes in "real time" did not occur until 1996, two years after the priority date of the Patents-in-Suit.

Defendants also disagree with Plaintiffs' statements regarding the alleged invention relating to the configuration of "hairpin structures." As discussed below, a hairpin structure does not require the presence of reporters or quenchers, nor does it require any particular relative position be adopted by a reporter and quencher.

III. ARGUMENT

A. APPLICABLE LEGAL PRINCIPLES

Although Plaintiffs have articulated several principles of claim construction, Defendants note several other important principles used in construing claim language. Disputed claim language is analyzed by first examining "the words of the claims themselves." *Innova/Pure*

Water Inc. v. Safari Water Filtration Sys. Inc., 381 F.3d 1111, 1115 (Fed. Cir. 2004). "[T]he claims themselves provide substantial guidance as to the meaning of particular claim terms." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1314 (Fed. Cir. 2005). A court uses both asserted and unasserted claims to interpret the meaning of another claim term. *Phillips*, 415 F.3d at 1314. "Because claim terms are normally used consistently throughout the patent, the usage of a term in one claim can often illuminate the meaning of the same term in other claims." *Id.*

Furthermore, "[a court] cannot look at the ordinary meaning of the term . . . in a vacuum. Rather, [it] must look at the ordinary meaning in the context of the written description and the prosecution history." *Phillips*, 415 F.3d at 1313 (quoting *Medrad, Inc. v. MRI Devices Corp.*, 401 F.3d 1313, 1319 (Fed. Cir. 2005)). Additionally, prior art cited in the prosecution history is considered intrinsic evidence. *Id.* at 1317 ("The prosecution history, which we have designated as part of the 'intrinsic evidence,' consists of the complete record of the proceedings before the PTO and includes the prior art cited during the examination of the patent.") (citing *Autogiro Co. of Am. v. United States*, 384 F.2d 391, 399 (Ct. Cl. 1967)).

Extrinsic evidence can also be used to "help educate the court regarding the field of the invention and can help the court determine what a person of ordinary skill in the art would understand claim terms to mean." *Phillips*, 415 F.3d at 1319.

B. CLAIM CONSTRUCTION DISPUTES

The parties dispute the construction of eight claim terms and request the Court's construction of these terms:

1. "Quencher Molecule"

Claim Phrase & Affected Claims	Defendants' Proposed Construction	Plaintiffs' Proposed Construction
quencher molecule '848 patent: 1-24 '591 patent: 1-15, 26-30 '930 patent: 1-17 '787 patent: 1-6 '659 patent: 1-36	a molecule that absorbs light at one wavelength and emits light at a different wavelength	a molecule capable of absorbing the fluorescence energy of an excited reporter molecule, thereby quenching the fluorescence signal that would otherwise be released from the excited reporter molecule

Defendants request the Court adopt their proposed construction of "quencher molecule" because it avoids the numerous problems that result from Defendants' proposed constructions, including nonsensical claims, meaningless claim limitations, redundancy, and ambiguity.

a. Terms Appearing in More Than One Claim Must Be Construed the Same For Each Claim, But That Construction Must Not Be Nonsensical.

The Federal Circuit has repeatedly upheld the principle that "if a claim term appears in more than one claim it should be construed the same in each." *Dayco Prods. Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1371 (Fed. Cir. 2003). Moreover, a claim cannot be interpreted in a way that makes another claim using that term in the same patent nonsensical. *See Schoenhaus v. Genesco, Inc.*, 440 F.3d 1354, 1357 (Fed. Cir. 2006) (holding that plaintiff's proposed construction in claim 1 cannot be correct because it renders claim 2 nonsensical, despite the specification specifically allowing for plaintiff's construction). "A claim construction that renders asserted claims facially nonsensical 'cannot be correct.'" *Becton, Dickinson & Co. v. Tyco Healthcare Group LP*, 616 F.3d 1249, 1255 (Fed. Cir. 2010) (quoting *Schoenhaus*, 440 F.3d at 1357); *see also Bd. of Regents of the Univ. of Tex. Sys. v. BenQ Am. Corp.*, 533 F.3d 1362, 1370 (Fed. Cir. 2008) ("We decline to adopt a construction that would effect this nonsensical result.").

b. Defendants' Construction is Necessary to Prevent a Nonsensical Result.

"Quencher molecule" must be construed the same across the claims of the Patents-in-Suit in a way that does not lead to a nonsensical result. Thus, Defendants' proposed construction is necessary in order to prevent other claims in the Patents-in-Suit from becoming nonsensical. Only by construing "quencher molecule" as a molecule emitting light do other claims in the Patents-in-Suit avoid being nonsensical.

For example, claim 24 of the '848 patent requires:

> the ratio of the fluorescence intensities of said reporter molecule to said quencher molecule when said probe is hybridized to said target polynucleotide being at least about a factor of 6 greater than the ratio of the fluorescence intensities of said reporter molecule to said quencher molecule when said probe is single-stranded.

(Pls.' Ex. A at col. 16, ll. 22-28.)[1] A simpler way of understanding this limitation is with the following formula: $\left(\frac{FIR}{FIQ}\right)_{hybridized} \geq 6\left[\left(\frac{FIR}{FIQ}\right)_{unhybridized}\right]$, where "FIR" is the fluorescence intensity of the reporter and "FIQ" is the fluorescence intensity of the quencher. A quencher molecule that does not emit light, *i.e.*, does not fluoresce, has a fluorescence intensity of zero (FIQ=0). If a quencher has zero fluorescence intensity, the ratio of the fluorescence intensities of a reporter and quencher will have a denominator value of zero. Dividing by zero is mathematically nonsensical and would make claim 24 nonsensical. This same nonsensical result would also occur in claim 15 of the '591 patent and claims 16, 17, and 39 of the '930 patent. Therefore, "quencher molecule" must be construed as a structure emitting light if the claims reciting ratios of fluorescence intensities of the reporter and quencher moieties are to avoid being nonsensical.

[1] Defendants will refer to the exhibits submitted by Plaintiffs' Claim Construction Brief as "Pls.' Ex. __" and will refer to Defendants' exhibits submitted herewith as "Defs.' Ex. __."

Plaintiffs' only argument in support of their proposed construction is that the specification for the Patents-in-Suit discloses quenchers that emit light and quenchers that do not emit light. Defendants do not dispute this. However, this does not overcome the fact that Plaintiffs' proposed construction creates a nonsensical result. In *Schoenhaus*, the Federal Circuit acknowledged that the patent specification clearly disclosed that the invention covered an "insert" or a "shoe." 440 F.3d at 1357. However, construing the term "orthotic device" as a shoe would have rendered one of the claims nonsensical, and so the Federal Circuit limited the construction to an "insert." *Id.* at 1357. Accordingly, the disclosure in the specification of quenchers that do not emit light does not mandate a claim construction encompassing quenchers that emit light and those that do not, because such a construction renders several claims nonsensical.

c. "Quencher Molecule" Must Be Interpreted to Require the Emission of Light or Claims Will Be Invalid.

As shown above, when a claim term is subject to two different interpretations and one of them would render claims invalid, the claim term is interpreted to preserve validity. In this case, while the specification discloses both fluorescent and non-fluorescent quencher molecules, any interpretation that includes non-fluorescent quenchers renders a claim "nonsensical" and thus invalid. It is well settled that "[c]laims amenable to more than one construction should, when it is reasonably possible to do so, be construed to preserve their validity." *Karsten Mfg Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1384 (Fed. Cir. 2001). Adherence to this settled rule requires that the claim term "quencher molecule" be interpreted to require the emission of light so as to provide non-zero values of the fluorescence intensity.

In fact, the prosecution history of the '930 patent reveals that even the examiner considered a ratio where the fluorescence intensity of the quencher is zero to be nonsensical. In

a January 21, 1997 office action, the examiner rejected a claim as indefinite under 35 U.S.C. § 112 for reciting a ratio limitation where a quencher did not emit light:

> Claim 17[2] is indefinite in the recitation of the ratio of fluorescent intensities of said reporter molecule to said ["]quencher molecule" in that the quencher molecule in this claim was not recited as being fluorescent so it is unclear what "intensities" are actually being compared to arrive at a ratio.

(Defs.' Ex. A at 4, ¶ c.) In response, Plaintiffs cured this deficiency by amending the claim to recite that the quencher molecule is fluorescent:

> With regard to claim 17, the Examiner objects that the quencher is not specified as being fluorescent. In response, Applicants amend claim 17 to specify a fluorescent quencher.

(Pls.' Ex. L at 11.)

Thus, Defendants' proposed construction is in accordance with the examiner's statements and should be adopted in order to avoid a construction that would invalidate claims as indefinite. Plaintiffs' amendment shows that Plaintiffs acquiesced to the examiner's statement. *See Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 234 F.3d 558, 566 (Fed. Cir. 2000) (en banc) (subsequent history omitted).

d. Defendants' Construction Prevents Claim Limitations From Being Rendered Meaningless.

In addition to avoiding a nonsensical result, Defendants' proposed construction prevents the claim limitations from becoming meaningless. Looking again at the mathematical representation $\left(\frac{FIR}{FIQ}\right)_{hybridized} \geq 6\left[\left(\frac{FIR}{FIQ}\right)_{unhybridized}\right]$, a ratio with zero in the denominator is equivalent to infinity, regardless of the numerator value. Thus, if the quencher does not emit light, the fluorescence intensity ratios at both the hybridized and unhybridized states would be

[2] Claim 17 was renumbered to claim 16 when the patent was allowed. Claim 16 of the '930 patent is asserted against Defendants.

infinity. No matter the numerator values, both ratios would always be equal to each other since both ratios would be infinity. Consequently, the claim limitation is always met for all values for the fluorescence intensity of the reporter. If all values for the fluorescence intensity of the reporter meet the claim limitation, then the limitation is meaningless.

Furthermore, Plaintiffs' construction results in a meaningless limitation, as is seen in claim 23 of the '848 patent. The claim requires "the fluorescence intensity of said reporter molecule is at least about a [factor of][3] 3.5 greater than the fluorescence intensity of said quencher molecule." (Pls.' Ex. A at col. 15, l. 35 – col. 16, l. 2.) This claim can be more simply conveyed as: $(FIR)_{hybridized} \geq 3.5(FIQ)_{hybridized}$. Because zero multiplied by anything is zero, the right side of the equation would always be zero for a quencher that does not emit light. Thus, **any** value for the fluorescence intensity of the reporter molecule (*i.e.*, the left side of the equation) would be greater or equal to zero and would meet this limitation, making this limitation meaningless. The same is true for claims 14 and 24 of the '591 patent and claims 15 and 37 of the '930 patent, which disclose fluorescence intensities of a factor of 3.5 greater than the fluorescence intensity of the quencher.

Therefore, the Court should apply Defendants' construction, which keeps claim limitations from becoming meaningless when quenchers do not emit light.

e. Plaintiffs' Construction Creates Redundancy and Ambiguity

Plaintiffs' construction is also highly redundant in view of the rest of the claim language. In every independent claim disclosing a "quencher molecule" in the Patents-in-Suit, the claim also recites that the quencher molecule quenches the fluorescence of a reporter molecule. *See* '848 patent, claims 1, 14, 24; '591 patent, claims 1, 15, 26, 30; '930 patent, claims 1, 16; '787

[3] The original claim language had "favor" instead of "factor of." This was corrected in the August 5, 1997 Certificate of Correction.

patent, claims 1, 7; and '569 patent, claim 1. Thus, construing "quencher molecule" to include that it quenches the fluorescence of a reporter molecule is redundant. The following chart substituting the proposed claim language in claim 1 of the '591 patent demonstrates this:

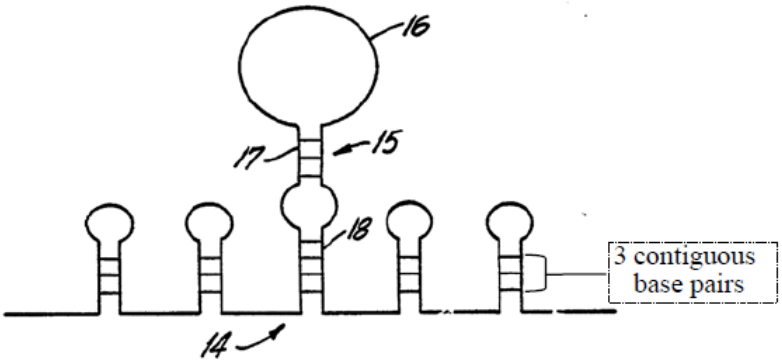
Original language of Claim 1 of '591 Patent	**Substitution of Defendants' Construction**	**Substitution of Plaintiffs' Construction**
a quencher molecule capable of quenching the fluorescence of said reporter molecule attached to said oligonucleotide sequence	[*a molecule that absorbs light at one wavelength and emits light at a different wavelength*] capable of quenching the fluorescence of said reporter molecule attached to said oligonucleotide sequence	[*a molecule capable of absorbing the fluorescence energy of an excited reporter molecule, thereby* ***quenching the fluorescence*** *signal that would otherwise be released from the excited reporter molecule*] capable of **quenching the fluorescence** of said reporter molecule attached to said oligonucleotide sequence

Substituting Plaintiffs' construction into the claim language unnecessarily repeats the recitation of the quencher's activity of quenching the fluorescence of a reporter. The claim language already describes that a quencher molecule quenches the fluorescence of a reporter molecule. Therefore, it is unnecessary to import that limitation into the construction of "quencher molecule." Moreover, Plaintiffs' construction adds ambiguity by introducing language that would need to be construed, *i.e.*, "excited." Defendants' construction does not create redundancies and does not introduce additional ambiguous language.

2. "A Hairpin Structure"

Claim Phrase & Affected Claims	**Defendants' Proposed Construction**	**Plaintiffs' Proposed Construction**
a hairpin structure '591 patent: 1-15, 26-30 '930 patent: 1-17 '787 patent: 1-6 '659 patent: 1-36	a single stranded oligonucleotide sequence that is hybridized with itself to form a double stranded duplex of 3 or more contiguous basepairs at the detection temperature of the assay	where the probe hybridizes to itself to form a loop such that the quencher molecule is brought into proximity with (next to) the reporter molecule in the absence of a complementary nucleic acid sequence to prevent the formation of the hairpin structure

Defendants' position is straightforward and based on the intrinsic record. In fact, the references cited by Plaintiffs as defining "a hairpin structure" show a single stranded oligonucleotide sequence that is hybridized with itself to form a double-stranded duplex of three or more contiguous basepairs:



(Defs.' Ex. B, Fig.4 (label added).) Furthermore, Plaintiffs are attempting to import extraneous limitations into the term. A hairpin structure requires the formation of a double-stranded oligonucleotide. Formation of a hairpin structure is dependent on the oligonucleotide sequence and independent of other components such as reporters and quenchers.

a. The Intrinsic Evidence Supports Hairpins Comprising At Least Three Basepairs.

Prior art cited in the prosecution history is intrinsic evidence. *Phillips*, 415 F.3d at 1317. The Plaintiffs incorporated WO 90/03446 into the specification for the definition of a hairpin and discussed it during prosecution. (*See* Pls.' Exs. B at col. 1, ll. 46-54; G at 2.) Accordingly, the reference is "intrinsic evidence" and it is proper to discuss it for claim construction purposes.[4]

The WO 90/03446 reference, which Plaintiffs cite for their construction (Pls.' Brief at 13), shows a wide variety of hairpin structures in the figures. It also shows hairpins of double-stranded oligonucleotides comprising three contiguous base pairs. Notably, the reference does

[4] The same is true for Defendants' Exhibit F.

not show any reporters or quenchers at all, much less any that are in "proximity" or "near to" each other. For example, the figure above plainly depicts single-stranded oligonucleotide sequences hybridized with themselves to form a double-stranded duplex of three or more contiguous basepairs and a single-stranded "loop."

Thus, despite Plaintiffs' assertion that "there is no intrinsic support for importing the '3 or more contiguous base pairs' limitation" (Pls.' Brief at 16), the intrinsic evidence clearly supports a construction allowing for 3 or more contiguous basepairs.

b. The Intrinsic Evidence Supports the Requirement of Detection Temperature.

Both basic science and the intrinsic evidence shows that a hairpin structure must be considered in context of the conditions which allow or disallow hairpin formation, *e.g.*, the ability of a single stranded oligonucleotide to form portions of double-stranded oligonucleotides, as depicted in the figure on the previous page. The main condition contributing to the ability of an oligonucleotide to form the double-strand necessary for a hairpin structure is temperature. If the temperature is too high, the self-complementary segments of the sequence will not hybridize to form a double-stranded structure. Similarly, if a hairpin structure containing a double-stranded portion is exposed to elevated temperature, the double-stranded segment will unhybridize or "melt." As Plaintiffs themselves admit in the specification, temperature is a factor that affects the ability of an oligonucleotide to form a double-stranded oligonucleotide (Pls.' Ex. C at col. 3, ll. 51-56.).

Plaintiffs' own claim terms support the construction that the probes do not form hairpin structures at the detection temperature. For example, claim 1 of the '930 patent states:

> **[M]onitoring** the fluorescence of said reporter molecule fluorescence intensity of said reporter molecule indicating the presence of said [sic] **under conditions where said oligonucleotide probe does not hybridize with itself to form a hairpin structure** in order to detect the hybridization of said target

polynucleotide to said oligonucleotide probe.

(Pls.' Ex. C at col. 23, ll. 46-52 (emphasis added).)

The prosecution history also supports Defendants' proposed construction. In the Notice of Allowability, the examiner stated that detection, *i.e.*, monitoring, occurs under conditions where the probe does not hybridize with itself:

> The following is an examiner's statement of reasons for allowance: . . . Fluorescence is **detected under conditions where said oligonucleotide probe does not hybridize with itself to form a hairpin structure** and provides a measure of hybridization of a target polynucleotide to the oligonucleotide probe.

(Pls.' Ex. M at 2 (emphasis added).)

Thus, the definition of "hairpin structure" includes the temperature at which the presence or absence of the hairpin structure is determined. Defendants' proposed construction reflects this reality while Plaintiffs' proposed construction ignores it.

c. Plaintiffs' Objections to Defendants' Proposed Construction Are Plainly Incorrect and Irrelevant.

Plaintiffs provide an illustration of the P2 probe – which shows four basepairs comprising the hairpin – and then argue that the limitation of "3 or more contiguous base pairs" "would read out probes taught in the asserted patents' examples which include overlapping sequences of four basepairs." (Pls.' Brief at 16.) Plaintiffs' argument is baffling. Defendants' proposed construction does not read out a probe with an overlapping sequence of four basepairs. A probe with four contiguous basepairs is obviously within the scope of "3 or more contiguous base pairs."

Also, Plaintiffs point to the descriptions of a hairpin structure in Biosearch's patents. (Pls.' Brief at 17.) However, Biosearch's patents are not intrinsic evidence. These descriptions of a hairpin are irrelevant to how hairpin structures are described in the Patents-in-Suit. Further, Plaintiffs did not cite this extrinsic evidence in the Joint Claim Construction and Prehearing

Statement (Dkt. No. 175-3) and it should not be considered. *See*, *e.g.*, *Aristocrat Techs. v. Int'l Game Tech.*, 2009 U.S. Dist. LEXIS 40975, at *9 (N.D. Cal. May 14, 2009).

d. Plaintiffs' Proposed Construction Is Redundant With the Claim Language.

Plaintiffs' proposed construction improperly imports limitations into the term "hairpin structure" that are redundant with the rest of the claim language. Plaintiffs' proposed construction assumes that both a reporter and a quencher are present, and secondly that when the probe is hybridized to itself, the reporter and quenchers are brought into "proximity" or "next to" each other. Plaintiffs rely on the prosecution history for support in adding the "proximity" and "next to" limitations to the claim construction. (Pls.' Brief at 14-15.) However, the term "hairpin structure," taken alone, does not speak to reporters or quenchers, nor does it speak to their relative proximity. Reporters and quenchers are not necessary to form hairpin structures. "Hairpin structure" relates solely to the structure of the oligonucleotide strand.

That reporters and quenchers are not included in the definition of "hairpin structure" is clear from looking at the relevant claims reciting the claim term: For example, claim 1 of the '930 patent provides for a "hairpin structure," but it also recites a "reporter molecule" and a "quencher molecule." (*See* Pls.' Ex. C at col. 23, ll. 25-45.) The claim also describes the positions of the reporter and quencher when attached to an oligonucleotide probe – "adopting at least one conformation when hybridized" – and when the oligonucleotide is "not hybridized with itself in the form of a hairpin structure." (*See id.*) It is improper for Plaintiffs to import limitations regarding the quencher molecule, reporter molecule, and their relative positions into the construction of "hairpin structure" when other limitations in the claims describe the quenchers and reporters and what their relative positions are.

e. Plaintiffs Rely On an Inadmissible Dictionary Definition at the Expense of the Intrinsic Record.

Plaintiffs' construction changes the phrase "brought into proximity with the reporter" (as was disclosed in the specification) to "brought into proximity **(next to)** with the reporter." (Pls.' Brief at 13 (emphasis added).) In support of this blatant and improper addition of a limitation, Plaintiffs rely on a definition from *Webster's International Dictionary* (3d ed. 1993). (Pls.' Brief at 15.) This extrinsic evidence was not included by Plaintiffs in the Joint Claim Construction and Prehearing Statement (Dkt. No. 175-3) and should not now be considered. *See*, *e.g.*, *Aristocrat Techs*, 2009 U.S. Dist. LEXIS 40975, at *9.

In summary, Defendants' proposed construction is supported by the intrinsic evidence, while Plaintiffs' proposed construction improperly adds limitations based on extrinsic evidence that should not even be considered. Accordingly, Defendants' construction should be adopted.

3. "Said Reporter/Quencher Molecule is Separated From Said Quencher/Reporter Molecule by at Least 15 Nucleotides"

Claim Phrase & Affected Claims	Defendants' Proposed Construction	Plaintiffs' Proposed Construction
said reporter/quencher molecule is separated from said quencher/reporter molecule by at least 15 nucleotides '848 patent: 4, 6, 15 '591 patent: 2, 4, 27 '930 patent: 3, 5 '787 patent: 3, 5	the reporter and quencher molecules are at least 15 nucleotides apart, inclusive of the nucleotides to which the reporter and quencher molecules are attached The interpretation will be applied to other claims with different numbers of nucleotides	one member of a reporter-quencher pair is attached to a nucleotide of the probe and the other member to a nucleotide at least 15 nucleotides away. This construction will be applied to other claims with different numbers of nucleotides

Defendants' construction follows the plain language of the claims and the specifications. For example, claim 4 of the '848 patent reads: "The method according to claim 1 wherein said reporter molecule is separated from said quencher molecule by at least about 15 nucleotides."

The plain language of claim 4 states that the reporter molecule and quencher molecule are separated by about 15 nucleotides. The same is true for all of the other affected claims.

Plaintiffs themselves suggest in their own specification the inclusion of both nucleotides that are attached to the reporter and quencher into the separation determination. For example,

> Doubly labeled probes were synthesized with 6-FAM-labeled phosphoramidite at the 5' end . . . . [P]robes are named by designating the sequence from Table 1 and the position of the LAN-TAMRA moiety. For example, probe Al-7 has sequence of Al with LAN-TAMRA at nucleoside position 7 from the 5' end.

(Pls.' Ex. A at col. 7, ll. 14-28.) Probe A1-7, referenced in the quote above, has a 5′ reporter (FAM) attached to the first 5′ terminal nucleotide and a quencher (TAMRA) attached to the 7th nucleotide, counting from the 5′ end. The following illustration shows where the reporter and quencher are attached to the A1-7 probe:

Thus, the naming of the probe A1-**7** indicates that **seven** nucleotides are counted, inclusive of the nucleotides to which the reporter and quencher are attached. Similarly, probe A3-6 has a 5′ reporter attached to the first 5′ terminal nucleotide and a quencher attached to the 6th nucleotide, counting from the 5′ end:

Thus, the very names of Plaintiffs' probes indicate that the nucleotides attached to the reporter and quencher are counted in determining the term "separated from."

Moreover, the specification supports Defendants' construction. In fact, the very language Plaintiffs quote supports Defendants' construction: "A separation of about 6-16 nucleotides . . . is typically achieved by attaching one member of a reporter-quencher pair to the 5′ end of the

probe and the other member to a base 6-16 nucleotides away." (Pls.' Brief at 18 (emphasis added).) "Probe" refers collectively to all the nucleotides that comprise a probe. The specification states that the other member of the reporter-quencher pair is attached "to a base 6-16 nucleotides away." (*See*, *e.g.*, Pls.' Ex. A at col. 2, l. 57.) What is the "away" in reference to? It makes no sense to be 6-16 nucleotides away from the probe because both members of the reporter-quencher pair are attached to the probe. Furthermore, nothing in this language indicates that the other member of the pair is 6-16 nucleotides away from the nucleotide attached to the first member of the pair. The only reasonable interpretation is that the other member of the pair is 6-16 nucleotides away from the "one member of a reporter-quencher pair," *i.e.*, the reporter or quencher. Nothing in the specification indicates that the nucleotide attached to the first member should not be counted.

Plaintiffs' proposed construction is also internally inconsistent. There is no reason why the nucleotide attached to the first member of the reporter-quencher pair would not be counted while the nucleotide attached to the other member of the reporter-quencher pair would be counted. Plaintiffs offer no explanation why only one attached nucleotide – and not both – should be ignored from the determination of the separation of the reporter and quencher. This inconsistency is further evidence that Plaintiffs' proposed construction is contrived.

Plaintiffs primarily support their construction with a single statement in the prosecution history of the '591 patent. However, this single example does not outweigh the clear language of the claims and the specification.

4. "Terminal Nucleotide"[5]

Claim Phrase & Affected Claims	Defendants' Proposed Construction	Plaintiffs' Proposed Construction
Terminal Nucleotide '848 patent: 8-13, 17-22 '591 patent: 6-11 '930 patent: 7-12	a terminal nucleotide unit that comprises a base, a ribose or deoxyribose structure and a phosphate or modified phosphate structure	No construction is required for this term.

Plaintiffs assert that Defendants' construction is too narrow and argue that the term should include "modified base and sugar moieties explicitly contemplated by the description of nucleotides in the specification." (Pls.' Brief at 20.) Plaintiffs further assert that Defendants' construction excludes "phosphodiester bonds or analogs thereof." (*Id.*) Defendants have no intention of excluding the modified moieties identified in the specification and do not believe their proposed construction excludes those modified moieties. However, Defendants would agree to an alternative construction that includes the modified moieties and that does not conflict with the specification or the file history.

5. "Monitoring the Fluorescence"

Claim Phrase & Affected Claims	Defendants' Proposed Construction	Plaintiffs' Proposed Construction
Monitoring the Fluorescence '848 patent: 1-24 '930 patent: 1-15 '787 patent: 1-6	monitoring the generation of fluorescence at a particular wavelength only at the conclusion of an amplification reaction	No construction is required for this term.

Defendants' construction accounts for the reality that "real time" monitoring of PCR using dual-labeled probes was not publicly available at the time of the invention. Dr. Livak, an inventor of the Patents-in-Suit, even admitted that "real time" monitoring was developed two

[5] Plaintiffs incorrectly claim that there is no genuine dispute regarding infringement or invalidity of the "terminal nucleotide" and "monitoring the fluorescence" claims. The construction of these claims directly relate to Defendants' defenses.

years after the filing date of the Patents-in-Suit. Therefore, the meaning of "monitoring the fluorescence" cannot now be broadened to capture this later-developed technology. Defendants' proposed construction accurately reflects what "monitoring the fluorescence" was understood to mean at the time of the filing of the Patents-in-Suit.

"A claim meaning cannot have different meanings at different times; its meaning must be interpreted as of the effective filing date." *PC Connector Solutions LLC v. SmartDisk Corp.*, 406 F.3d 1359, 1363 (Fed. Cir. 2005). "[T]he ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Phillips*, 415 F.3d at 1313. "When a claim term understood to have a narrow meaning when the application is filed later acquires a broader definition, the literal scope of the term is limited to what it was understood to mean at the time of filing." *PC Connector*, 406 F.3d at 1363 (quoting *Kopykake Enters., Inc. v. Lucks Co.*, 264 F.3d 1377, 1383 (Fed. Cir. 2001)).

Because the Patents-in-Suit claim priority to the '848 patent, the relevant date for determining the ordinary and customary meaning of "monitoring the fluorescence" is November 16, 1994, the filing date of the '848 patent. At that time, the only way to monitor the generation of fluorescence during PCR analysis using dual-labeled probes was through "end point analysis," *i.e.*, taking measurements only at the end of an amplification reaction. Real time monitoring of fluorescence in PCR using dual-labeled probes was not publicly available until two years later. Therefore, allowing "monitoring the fluorescence" to include real time monitoring impermissibly broadens the meaning of the claim term beyond what the term was understood to mean in November 1994 to persons of ordinary skill in the art. Defendants' proposed construction accurately defines what "monitoring the fluorescence" meant at the relevant date.

a. Inventor Statements and Assignee Statements Are Particularly Useful for Determining How the Claim Term Was Understood to a Person of Ordinary Skill in the Art.

While extrinsic evidence is not favored in some circumstances, it can be used to "help educate the court regarding the field of the invention and can help the court determine what a person of ordinary skill in the art would understand claim terms to mean." *Phillips*, 415 F.3d at 1319. Moreover, inventors are particularly competent witnesses to explain their own inventions:

> Patents are written not for laymen, but for and by persons experienced in the field of the invention. An inventor is a competent witness to explain the invention and what was intended to be conveyed by the specification and covered by the claims. . . . Although *Markman* and other precedent caution the court against creative reconstruction of an invention by interested persons, courts are not novices in receiving and weighing expertise on both sides of an issue. The Supreme Court in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 125 L. Ed. 2d 469, 113 S. Ct. 2786 (1993) instructed trial judges to exclude scientifically unqualified witnesses, not those with superior qualifications.

See Voice Technologies Group, Inc. v. VMC Sys., Inc., 164 F.3d 605, 615-16 (Fed. Cir. 1999).

In this case, statements made in a 1996 paper co-authored by lead inventor Dr. Livak show that, two years after the filing date of the '848 patent, Dr. Livak considered the ability to perform real time PCR using dual-labeled probes as a "novel" breakthrough:

> **We have developed a novel "real time" quantitative PCR method.** The method measures PCR product accumulation through a dual-labeled fluorogenic probe (i.e. TaqMan Probe). This method provides very accurate and reproducible quantitation of gene copies. Unlike other quantitative PCR methods, real-time PCR does not require post-PCR sampling handling, preventing potential PCR product carry-over contamination and resulting in much faster and higher throughput assays.

(Defs.' Ex. C at 986 (emphasis added).) The paper then states:

> The approach uses dual-labeled fluorogenic hybridization probes . . . . One fluorescent dye serves as a reporter [FAM (i.e., 6-carboxyfluorescein)] and its emission spectra is quenched by the second fluorescent dye, TAMRA (i.e., 6-carboxy-tetramethyl-rhodamine). The nuclease degradation of the hybridization probe releases the quenching of the FAM fluorescent emission, resulting in an increase in peak fluorescent emission at 518 nm. The use of a sequence detector (ABI Prism) allows measurement of the fluorescent spectra of all 96 wells of the thermal cycler continuously during the PCR amplification. **Therefore, the reactions are monitored in real time.**

(*Id.* at 987 (emphasis added).) These statements show that Dr. Livak did not consider real time PCR monitoring to be within the scope of the original invention because he came up with it only after having access to the ABI Prism machine.

Additionally, statements from the assignee of the patents, ABI, are consistent with Dr. Livak's paper. ABI wrote a review in 2006 stating:

> In 1996, Applied Biosystems introduced the world to real-time PCR with the release of the ABI Prism 7700 sequence detection system. About this time, TaqMan® assay chemistry, a PCR analysis technique used with this system for measuring gene expression, was also developed with strategic partner Roche Molecular Systems (Alameda, CA).

(Defs.' Ex. D at 3.)

Taken together, these statements describe the field of the invention and reveal that a person of ordinary skill in the art in 1994 would understand "monitoring the fluorescence" to exclude real time analysis.

b. The Specification Shows That Real Time Monitoring Was Merely a Desire but Not Reality.

The specification of the Patents-in-Suit shows that the inventors desired real time analysis for PCR using dual-labeled probes, but that it was not a reality at the time the '848 patent application was filed. For example, they state in the Background of the Invention:

> In particular, the design of instruments permitting amplification to be carried out in closed reaction chambers and monitored in real time would be highly desirable for preventing cross-contamination, . . . Clearly, the successful realization of such a design goal would be especially desirable in the analysis of diagnostic samples, where a high frequency of false positives and false negatives–caused by "sample carryover"–would severely reduce the value of an amplification procedure.

(*See* Pls.' Ex. A at col. 1, l. 33-42.) Therefore, the inventors – and any person of ordinary skill in the art – would have understood the "monitoring the fluorescence" of dual-labeled probes claim language not to cover "real time" monitoring.

c. Plaintiffs Attempt to Interpret "Monitoring the Fluorescence" in a Vacuum.

Plaintiffs argue that the term "monitoring the fluorescence" does not require construction as the term is "plain, simple and readily understood by the finder of fact." (Pls.' Brief at 21.) However, the Federal Circuit makes clear that a court "cannot look at the ordinary meaning of the term . . . in a vacuum. Rather, [it] must look at the ordinary meaning in the context of the written description and the prosecution history." *Phillips*, 415 F.3d at 1313. Further, the proper meaning of the term is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." *Id.* Using the rhetoric of plain and simple language, Plaintiffs improperly attempt to capture later-developed technology that was not understood to be encompassed by "monitoring the fluorescence" at the time of the invention.

In sum, both the intrinsic and extrinsic evidence shows that Defendants' proposed construction accurately reflects what "monitoring the fluorescence" meant to a person of ordinary skill in the art at the time of the filing of the Patents-in-Suit.

C. Means-Plus-Function and Step-Plus-Function Claims.[6]

The remaining claim terms to be construed are means-plus-function or step-plus-function, despite the fact that they lack "means" and "step for" language. While a claim limitation that does not contain "means" language creates a presumption that § 112, ¶ 6 does not apply, "it is not the end of the inquiry." *Mas-Hamilton Group v. La Gard, Inc.*, 156 F.3d 1206, 1213 (Fed. Cir. 1998). The presumption can be rebutted if "the claim term fails to recite sufficiently definite structure or else recites a function without reciting sufficient structure for performing that

[6] Although Plaintiffs assert that Defendants have waived § 112, ¶ 6 constructions (Pls.' Brief at 24 n.6), Plaintiffs received adequate notice of Defendants' § 112, ¶ 6 constructions in Defendants' Proposed Claim Terms, Phrases, and Clauses for Construction, served February 4, 2011. (Defs.' Ex. E.) *See 3M Co. v. Moldex-Metric, Inc.*, 641 F. Supp. 2d 834, 839 (D. Minn. 2009).

function." *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1369 (Fed. Cir. 2002) (quoting *Watts v. XL Sys., Inc.*, 232 F.3d 877, 880 (Fed. Cir. 2000) (internal quotes omitted).

Similarly, for method claims, if the claim limitation does not contain "step for" language, the presumption that § 112, ¶ 6 does not apply can be overcome with a showing that the limitation contains no "act." *See Masco Corp. v. United States*, 303 F.3d 1316, 1327 (Fed. Cir. 2002). In a concurrence opinion, Judge Rader explained that the function of a method claim element corresponds to "what that element ultimately accomplishes in relationship to what the other elements of the claim and the claim as a whole accomplish." *Seal-Flex, Inc. v. Athletic Track & Court Constr.*, 172 F.3d 836, 849 (Fed. Cir. 1999). In contrast, acts correspond to "how the function is accomplished." *Id*. at 849-50.

"[A]s a matter of statutory authority, a claim term will cover nothing more than the corresponding structure or step disclosed in the specification, as well as equivalents thereto, if the patentee phrased the claim in step- or means-plus-function format." *CCS Fitness*, 288 F.3d at 1367.

1. "Said oligonucleotide probe/sequence existing in/is capable of adopting at least one single-stranded conformation when unhybridized/not hybridized to said target polynucleotide where said quencher molecule quenches the fluorescence of said reporter molecule, said oligonucleotide probe/sequence existing in/is capable of adopting at least one conformation when hybridized to said target polynucleotide where the fluorescence of said reporter molecule is unquenched"

Claim Term & Affected Claims	Defendants' Proposed Construction	Plaintiffs' Proposed Construction
said oligonucleotide probe/sequence existing in/is capable of adopting at least one single-stranded conformation when unhybridized/not hybridized to said target polynucleotide where said quencher molecule quenches	Means + function/steps + function without acts interpretation As this is a functional limitation, the law states that only structures that correspond to the function	Plaintiffs are of the view that no construction is required for this term. Should the Court decide a construction is required, Plaintiffs believe that it

the fluorescence of said reporter molecule, said oligonucleotide probe/sequence existing in/is capable of adopting at least one conformation when hybridized to said target polynucleotide where the fluorescence of said reporter molecule is unquenched '848 patent: 1-24 '591 patent: 1-15, 26-30 '930 patent: 1-17 '787 patent: 1-6	are covered by the claims. However, there is no "corresponding structure" disclosed; as such, the claim term is indefinite and thus any claim containing it is invalid.	should be construed to have its plain and ordinary meaning.

The claim limitation describes the following function: existing in/is capable of adopting at least one single-stranded conformation when unhybridized/not hybridized to said target polynucleotide where the quencher quenches the fluorescence of the reporter molecule, and existing in/capable of adopting at least one conformation when hybridized to said target polynucleotide where the fluorescence of the reporter is unquenched. More simply, the function relates to existing in or adopting different conformations such that each conformation has an effect on quenching.

In *Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc.*, 422 F. Supp. 2d 446, 459 (D. Del. 2006), the court held that the presumption against the application of § 112, ¶ 6 for the term "soft start circuit" was rebutted. The court stated that a soft start circuit "encompass[ed] a variety of different possible structures and that those possible structures are not sufficiently identifiable from the claim language." *Id.* at 460. Here, the means for the function is an oligonucleotide sequence or probe[7]. Like a circuit, an oligonucleotide probe/sequence can encompass a bewildering variety of different sequences. For example, a probe that is fifteen

[7] A nucleotide probe is synonymous with a nucleotide sequence. (*See*, *e.g.*, Pls.' Ex. A at Table 1.) "Probe" is a functional description of what the sequence does and does not denote any structure.

nucleotides long[8] has 4^{15} (or 1,073,741,824) possible sequences.[9] A person of ordinary skill in the art reading the claim would not be able to identify what the sequences are for performing the recited function.

Plaintiffs argue that the claim language is "replete with structural elements" and identifies terms such as "single-stranded conformation," "target polynucleotide," "quencher molecule," and "reporter molecule." (Pls.' Brief at 24.) However, none of these are structures for performing the function and are, therefore, irrelevant.

With respect to the method claims at issue, they are step-plus-function claims under § 112, ¶ 6. There are no acts disclosed in the claim limitation for carrying out the function. The function, *i.e.*, "what" is being accomplished, is a change in conformation that has an effect on the quenching. However, there are no acts disclosed on "how" to accomplish that function of changing the conformation.

Because § 112, ¶ 6 applies and no corresponding structures or acts are disclosed within the patent, this claim term is indefinite.

2. "The fluorescence intensity of said reporter molecule when said oligonucleotide sequence is hybridized to said target polynucleotide is at least a factor of 6 greater than the fluorescence intensity of said reporter molecule when said oligonucleotide sequence is not hybridized to said target polynucleotide"

Claim Term & Affected Claims	**Defendants' Proposed Construction**	**Plaintiffs' Proposed Construction**
the fluorescence intensity of said reporter molecule when said	<u>Means + function interpretation</u> As this is a functional limitation, the law states that only corresponding structures are covered by the	Plaintiffs are of the view that no construction is required for this

[8] A probe that is 15 nucleotides long is a conservative example. Several of the asserted claims cover probes as long as 60 nucleotides. (*See*, *e.g.*, Pls.' Ex. A, claims 5 and 16.)

[9] There are four possible nucleotides for each position. Thus the total number of possible sequences for a probe 15 nucleotides long would be 4^{15}.

oligonucleotide sequence is hybridized to said target polynucleotide is at least a factor of 6 greater than the fluorescence intensity of said reporter molecule when said oligonucleotide sequence is not hybridized to said target polynucleotide '591 patent: 1-14	claims. In this case, as stated by the patentee, the only structure identified by patentee as corresponding to this limitation is probe P2-27, a specific probe of 27 nucleotides with a 5' FAM (reporter) and a 3' TAMRA (quencher). Therefore, the claims containing this term are limited to the use of the P2-27 probe. <u>Alternative Interpretations</u> In the event that this clause is not found to invoke §112, 6th paragraph, alternative interpretations are proposed: 1. As noted by patentee, probe P2-27 of Table 3 ('848 patent) meets this limitation. However, the conditions under which the data of Table 3 were run are not outlined. As is well known, the fluorescence properties of fluorophores attached to oligonucleotides vary widely based on a number of things including solution conditions, linkers and composition of the fluorophores. As testing conditions are not outlined, the claim term is too indefinite and ambiguous to interpret. 2. (FIR)hybridized $\geq$ 6(FIR)unhybridized "FIR" is the "fluorescence intensity of the reporter" The only conditions outlined in the patent are for the data generated in Table 2 ('848 patent) as follows. The FIR measurements are done in a solution of 10 mM Tris-HCl (pH 8.3), 50 mM KCl and 4 μM MgCl2. The FIR measurement is done by exciting the complex at the reporter's excitation maxima and detecting at the reporter's emission maxima. The measurements are done in this solution with 50 nM of the probe, and then with the addition of 100 nM target sequence.	term. Should the Court decide a construction is required, Plaintiffs believe that it should be construed to have its plain and ordinary meaning.

This claim limitation is a functional limitation describing the relative fluorescence intensity levels between a hybridized and unhybridized oligonucleotide sequence. Here, the function is changing the fluorescence intensity of a reporter molecule.

However, the claim term fails to recite sufficiently definite structure and recites function without reciting sufficient structure for performing that function. Similar to the claim limitation above in section C.1., an "oligonucleotide sequence" is not sufficient structure for performing the

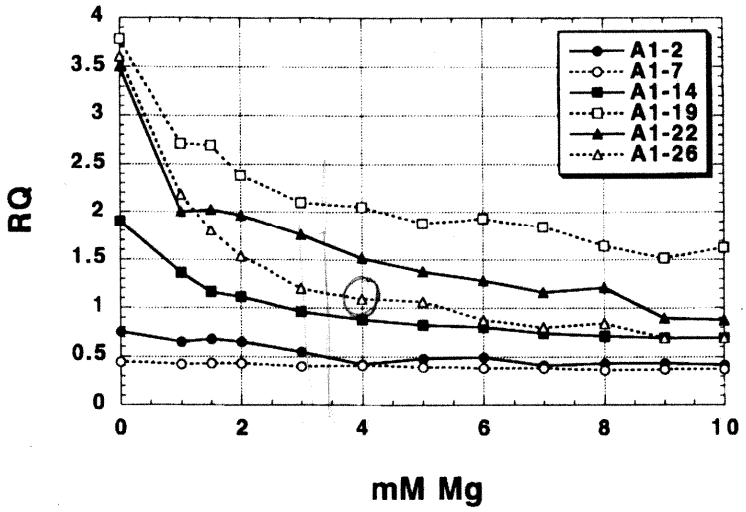
function because a numerous variety of oligonucleotide sequences can be encompassed. *See Power Integrations,* 422 F. Supp. 2d at 459-60. Furthermore, a person of ordinary skill in the art reading the claim would not be able to identify what oligonucleotide sequences would perform the recited function.

Accordingly, this claim term is limited to the corresponding structures identified in the patent for performing this function. The only corresponding structure identified in the Patents-in-Suit is the P2-27 probe. (*See* Pls.' Ex. K at 11 ("This feature of the probes of the present invention is shown in Table 3 of the parent application, entry P2-27.").)

Should the Court determine that § 112, ¶ 6 does not apply, Biosearch proposes alternative interpretations. First, the claim limitation is indefinite because fluorescence intensities vary widely with different conditions. For example, if the solution conditions are changed, the fluorescence intensities can also change, even with the same reporter molecule, oligonucleotide sequence, and polynucleotide sequence. Without specifying the conditions, this claim is indefinite. *See All Dental Prodx., LLC v. Advantage Dental Prods., Inc.*, 309 F.3d 774, 779-80 (Fed. Cir. 2002) ("The primary purpose of the definiteness requirement is to ensure that the claims are written in such a way that they give notice to the public of the extent of the legal protection afforded by the patent, so that interested members of the public, e.g., competitors of the patent owner, can determine whether or not they infringe.")

A paper written by inventor Dr. Livak and cited in the prosecution history of the Patents-in-Suit supports Defendants' proposed construction. *See Voice Technologies Group*, 164 F.3d at 615-16. In the journal article reporting the results outlined in the Patents-in-Suit, Dr. Livak stated that varying the magnesium concentration of the solution drastically alters the fluorescence intensities of the reporters and quenchers. (*See* Defs.' Ex. F at 361, Fig. 3.) The

following figure demonstrates how magnesium salt concentration has a powerful effect on fluorescence intensity:



The title of the figure is "Effect of Mg^{2+} concentration on RQ ratio for the A1 series of probes." As shown in the figure, the ratio of fluorescence intensity of the Reporter (R) to the fluorescence intensity of the quencher (Q), depicted in the figure as "RQ," changes from as high as about 3.75 at low magnesium concentration, to about 1.75 at higher magnesium concentration for the A1-26 probe, which is one of the probes described in the Patents-in-Suit.

If varying the salt concentration results in a two-fold change in the property specifically claimed in the asserted patents, a person of ordinary skill in the art would be unable to determine the proper conditions to ascertain infringement. Thus, the claim term is indefinite.

A second alternative construction is: $(FIR)_{hybridized} \geq 6(FIR)_{unhybridized}$, where "FIR" is the "fluorescence intensity of the reporter." This construction incorporates all of the elements of the claim term in a mathematical formula. Because the fluorescence intensities vary depending on the conditions, this alternative construction is limited to the conditions disclosed for the results in Table 2 of the '848 patent.

3. "The ratio of the fluorescence intensities of said reporter molecule to said quencher molecule when said probe is hybridized to said target polynucleotide being at least about a factor of 6/is at least 6 times greater than the ratio of the fluorescence intensities of said reporter molecule to said quencher molecule when said probe is single-stranded/said oligonucleotide sequence is not hybridized to said target polynucleotide"

Claim Phrase & Affected Claims	Defendants' Proposed Construction	Plaintiffs' Proposed Construction
the ratio of the fluorescence intensities of said reporter molecule to said quencher molecule when said probe is hybridized to said target polynucleotide being at least about a factor of 6/is at least 6 times greater than the ratio of the fluorescence intensities of said reporter molecule to said quencher molecule when said probe is single-stranded/said oligonucleotide sequence is not hybridized to said target polynucleotide" '848 patent: 24 '591 patent: 15 '930 patent: 17	Means + function/steps + function without acts interpretation As this is a functional limitation, the law states that only corresponding structures are covered by the claims. In this case, as stated by the patentee, the only structure corresponding to this limitation is probe A1-26, a specific probe of 26 nucleotides with a 5' FAM (reporter) and a 3' TAMRA (quencher). Therefore, the claims containing this term are limited to the use of the A1-26 probe. Alternative Interpretations In the event that this clause is not found to invoke §112, 6th paragraph, alternative interpretations are proposed: 1. As noted by patentee, probe A1-26 of Table 3 ('848 patent) meets this limitation. However, the conditions under which the data of Table 3 were run are not outlined. As is well known, the fluorescence properties of labeled probes vary widely based on a number of things including solution conditions and composition. As testing conditions are not outlined, the claim term is too indefinite and ambiguous to interpret. 2. [FIR/FIQ]hybridized $\geq$ 6([FIR/FIQ]unhybridized) "FIR" is the "fluorescence intensity of the reporter", and "FIQ" is the "fluorescence intensity of the quencher" The only conditions outlined in the patent are for the data generated in Table 2 ('848 patent) as follows. The measurements are done in a solution of 10 mM Tris-HCl (pH 8.3), 50 mM KCl and 4	Plaintiffs are of the view that no construction is required for this term. Should the Court decide a construction is required, Plaintiffs believe that it should be construed to have its plain and ordinary meaning.

	μM MgCl2. The FIR measurement is done by exciting the complex at the reporter's excitation maxima and detecting at the reporter's emission maxima. The FIQ measurement is done by exciting the complex at the reporter's excitation maxima and detecting at the quencher's emission maxima. The measurements are done in this solution with 50 nM of the probe, and then with the addition of 100 nM target sequence.	

Similar to the claim limitation above at section C.2., this claim limitation is a functional description of relative fluorescence intensity levels. This claim limitation compares the ratios of the fluorescence intensities of the reporter and quencher molecules when the oligonucleotide sequence is hybridized and not hybridized. Accordingly, the function described in this claim is changing the ratio of fluorescence intensities.

Sufficient structure for performing the function is not recited in the claim. The only possible structure for performing the function is an "oligonucleotide sequence" or "oligonucleotide probe." But for the same reasons described above for the claim terms in sections C.1. and C.2., an "oligonucleotide sequence" or "oligonucleotide probe" can "encompass[] a variety of different possible structures and [] those possible structures are not sufficiently identifiable from the claim language." *Power Integrations,* 422 F. Supp. 2d at 460. Thus, this claim element is means-plus-function pursuant to § 112, ¶ 6. The only structure in the patent specifications for this function is probe A1-26. Thus, the claim limitation is limited to the A1-26 probe. (*See* Pls.' Ex. K at 11 ("These claims are supported in the parent application at page 12, Table 3, A1-6 [sic].").)

With respect to the method claims reciting this claim limitation, they are step-plus-function claims. As stated above, the function for this limitation is changing the ratio of fluorescence intensities. However, there is no act corresponding to how that function is

accomplished. Accordingly, we look to the specifications of the patents in suit for the corresponding act. The only act disclosed is the use of the A1-26 probe, to which this claim term is limited.

Should the Court determine that § 112, ¶ 6 does not apply, Defendants propose two alternative interpretations. The first construction is that the term is too indefinite to interpret, since varying the conditions of the assay results in such different conditions that one of ordinary skill in the art would not know whether or not there is infringement. As described above, varying concentrations of magnesium will result in very different ratios of fluorescence intensity levels of the reporter and quencher molecules.

A second alternative construction is: $\left(\frac{FIR}{FIQ}\right)_{hybridized} \geq 6\left[\left(\frac{FIR}{FIQ}\right)_{unhybridized}\right]$, where "FIR is the "fluorescence intensity of the reporter," and "FIQ" is the "fluorescence intensity of the quencher." This construction incorporates all the elements of the claim term in a mathematical formula. Also, the same issue regarding variability of fluorescence intensities depending on the conditions, as described above in section C.2., applies here. Thus, this alternative construction is limited to the conditions for the results in Table 2 of the '848 patent.

IV. CONCLUSION

Defendants' proposed constructions take into account the entire intrinsic record, as well as extrinsic evidence when particularly applicable, to convey an accurate interpretation of the claim terms. Plaintiffs, in contrast, rely on simple citations to the specification and the rhetoric of "plain and ordinary meaning" for constructions that the full record reveals as less accurate than Defendants' constructions. For all of the reasons discussed above, Defendants respectfully request that the Court adopt Defendants' proposed constructions for the disputed claim terms.

Dated: July 1, 2011

Respectfully submitted,

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CERTIFICATE OF SERVICE

I certify that a true and correct copy of the foregoing document has been served on all counsel of record via the Court's Case Management/Electronic Case Filing system and/or electronic mail on July 1, 2011.

/s/ Daniel Johnson, Jr.
Daniel Johnson, Jr.